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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/760,574	01/16/2001	Jean-Christophe Francis Audonnet	454313.3154.1	2896

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FROMMER LAWRENCE & HAUG
745 FIFTH AVENUE- 10TH FL.
NEW YORK, NY 10151

EXAMINER	
ANGELL, JON E	

ART UNIT	PAPER NUMBER
1635	

DATE MAILED: 08/03/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/760,574	AUDONNET ET AL.	
	Examiner	Art Unit	
	Jon Eric Angell	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *25 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *84-118* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *84-118* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *16 January 2001* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Response to Amendment

This Action is in response to the communication filed on 6/25/04. The amendment has been entered. Claims 84-113 are currently pending in the application and are addressed herein. It is noted that claim 84 has been amended such that the claims is now limited to A DNA vaccine against a bovine pathogen wherein the bovine pathogen is BRSV, BVDV-1, BVDV-2, or bPI-3. A species election was previously set forth and applicants' elected the species BRSV for examination. The species election requirement is still proper, therefore, the instant claims are examined to the extent they read on the elected species (A DNA vaccine against BRSV).

Applicant's arguments are addressed on a per section basis. The text of those sections of Title 35, U.S. Code not included in this Action can be found in a prior Office Action. Any rejections not reiterated in this action have been withdrawn as being obviated by the amendment of the claims and/or applicant's arguments.

The finality of the Office Action is withdrawn in view of the new rejections set forth below, which were not necessitated by amendment.

Information Disclosure Statement

The information disclosure statement (IDS) submitted on 6/25/04 is acknowledged. The submission is in compliance with the provisions of 37 CFR 1.97. Accordingly, the information disclosure statement is being considered by the examiner.

Claim Rejections - 35 USC § 103

The claims rejected under 35 USC 103 have been withdrawn because the claims have been amended such that they no longer encompass a DNA vaccine against BHV, which is the DNA vaccine taught by Cox. Therefore, the Cox reference is no longer applicable and all rejections based on Cox are withdrawn.

Double Patenting

The provisional double patenting rejection of claims 84-118 of the instant application as being obvious variations of claims in co-pending application 09/766,422 has been withdrawn. The claims of the co-pending application are drawn to a method for obtaining an immune response by administering a DNA vaccine against a bovine or porcine pathogen in combination with a cationic lipid having a given structure and also administering a subunit or recombinant vaccine against a bovine or porcine pathogen. Therefore the claims in the co-pending application are drawn to a method wherein three elements are administered to a bovine or porcine animal while the claims of the instant application are drawn to only administering a DNA vaccine against BRSV, BVDV-1, BVDV-2 or bPI-3 in combination with a cationic lipid having a specific structure (i.e., without the additional sub-unit or recombinant vaccine). Since it is deemed that it would not have been obvious to administer the additional subunit/recombinant vaccine with the instantly claimed combination, the provisional obvious-type double patenting rejection is withdrawn.

Claims 84, 85, 96 and 116-117 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 5-8 of U.S. Patent No.

6,376,473 B1 (Audonnet) in view of in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) for the reasons of record.

Claims 84-91 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 5-8 of U.S. Patent No. 6,376,473 B1 (Audonnet) in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Xiang et al. (Immunity 1995, 2:129-135), and Baker et al. (US Patent 5,106,733; 1992) for the reasons of record.

Claims 84, 92, 94, 95, 100 and 108 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 5-8 of U.S. Patent No. 6,376,473 B1 (Audonnet) in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Li (WO 96/40945) for the reasons of record.

Claims 84, 93, 97, 98 and 104 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 5-8 of U.S. Patent No. 6,376,473 B1 (Audonnet) in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Choi et al. (Virology 1998, 250:230-240) for the reasons of record.

Claims 84-118 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 5-8 of U.S. Patent No. 6,376,473 B1 (Audonnet) in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Xiang et al. (Immunity 1995, 2:129-135), Baker et al. (US Patent

5,106,733; 1992), Li (WO 96/40945), and Choi et al. (Virology 1998, 250:230-240) for the reasons of record.

The response to Applicants' arguments is found following the new rejections below.

NEW GROUNDS OF REJECTION

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 84, 85, 96 and 116-118 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 5-8 of U.S. Patent No. 6,376,473 B1 (Audonnet) in view of U.S. Patent No. 6,586,409 B1 (Wheeler).

It is noted that the invention appears to be an improved vaccine for a bovine pathogen (BRSV) wherein the improvement is the addition of a lipid complex (such as DMRIE/DOPE) to the vaccine. As mentioned below, a DNA plasmid vaccine for BRSV was known in the prior art (Audonnet) and the lipid complex DMRIE/DOPE was known to act as an adjuvant as well as a

facilitator of DNA delivery into cells (Klavinskis). Therefore, for the reasons set forth below, the instant claims are obvious in view of the prior art.

The claims are drawn to a DNA vaccine against BRSV comprising at least one plasmid that contains and expresses in a bovine host cell a nucleotide sequence encoding a BRSV immunogen and a cationic lipid (see claims 84, 85, 112, 118); wherein the vaccine further comprises DOPE (claims 85, 112); wherein the bovine pathogen is BRSV (see claim 96); wherein the immunogen is BRSV-F (claim 116) or BRSV-G (claim 118).

Audonnet teaches a vaccine for BRSV comprising at least one plasmid that contains and expresses in vivo (in a bovine host cell) a nucleic acid molecule having sequences encoding BRSV-F, or BRSV-G or BRSV-F and –G proteins (e.g., see abstract and claims 5-8).

Audonnet does not teach that the BRSV vaccine comprises the cationic lipid DMRIE or DOPE, or the cationic lipid complex DMRIE/DOPE.

Wheeler teaches an adjuvant composition comprising a lipid or lipid complex (specifically DMRIE and DMRIE/DOPE, as well as GAP-DMRIE and DOPE) that can be used in combination with a DNA vaccine such as a plasmid vaccine wherein the lipid complex enhances the delivery and immune response to the polynucleotide-based vaccine. Specifically Wheeler teaches, "The adjuvant composition of the instant invention enhances the immune response of the vertebrate to the immunogen." (See col. 2, lines 55-61); and , "The present invention, in contrast to the prior art, is useful for enhancing the humoral response of a vertebrate to a polynucleotide-based vaccine..." (See col. 3, lines 27-30). With respect to the term "vertebrate", Wheeler specifically indicates, "The term 'vertebrate' is intended to encompass a singular 'vertebrate' as well as plural 'vertebrates', and comprises mammalian and avian species

as well as fish." (See col. 12, lines 35-40). Thus specifically indicating that the composition works in all mammals as well as fish and birds.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to combine the teachings of Audonnet and Wheeler to create the invention of the instant claims with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to combine the references in order to increase the uptake of the plasmid vaccine into the target cells—resulting in the increased expression of the encoded pathogens (here, BRSV-F and/or BRSV-G) and to stimulate the host's immune system in order to get an increased immune response against the pathogens.

Claims 84-91 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 5-8 of U.S. Patent No. 6,376,473 B1 (Audonnet) in view of U.S. Patent No. 6,586,409 B1 (Wheeler) and further in view of Xiang et al. (Immunity 1995, 2:129-135), and Baker et al. (US Patent 5,106,733; 1992) for the reasons of record.

It is noted that the instant claims appear to be drawn to an improved vaccine for a bovine pathogen (BRSV) wherein the improvement is the addition of a lipid complex (such as DMRIE/DOPE) to the vaccine (as mentioned above) with the addition of bovine GM-CSF or a plasmid encoding bovine GM-CSF to the vaccine. However, GM-CSF was known to act as an adjuvant for vaccine compositions. Therefore, for the reasons set forth below, the instant claims are obvious in view of the prior art.

Claims 84 and 85 are obvious in view of the teachings of Audonnet and Wheeler as mentioned above.

As mentioned above, Audonnet teaches a BRSV plasmid vaccine and Wheeler teaches lipid complexes which can be used to increase plasmid uptake and also as an adjuvant in a vaccine composition.

Neither Audonnet nor Wheeler teaches that the vaccine composition can comprise bovine GM-CSF or a plasmid encoding bovine GM-CSF.

Xiang teaches a method for enhancing the immune response to a DNA vaccine by co-administering a plasmid vaccine (here, a plasmid expressing the glycoprotein of rabies virus in vivo) and a plasmid expressing GM-CSF (here, mouse GM-CSF) (see p. 129, abstract; p. 130, Table 1; and p.132, under "A plasmid vector expressing mouse GM-CSF enhances the efficacy of the DNA vaccine to Rabies Virus). Xiang teaches that the mouse GM-CSF enhances the efficacy of the vaccine (see p. 132).

Xiang does not teach that the GM-GMCSF is bovine GM-CSF.

Baker teaches the cDNA sequence of bovine GM-CSF and methods of expressing bovine GM-CSF in a cell using an expression vector as well as methods for purifying the recombinant bovine GM-CSF (see Figure 1; column 1, lines 55-68; and column 6, line 13 through column 8, line 70). Baker teaches that bovine GM-CSF can be useful as "a therapeutic agent treating various cytopenias, and its apparent effect upon mature granulocytes and macrophages... [and] therapeutic compositions comprising recombinant bGM-CSF or active homologues could be employed to augment immune responsiveness to infectious pathogens or to assist in

reconstituting normal blood cell populations following viral infection or other conditions resulting in hematopoietic cell suppression." (See column 1, lines 41-53).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to combine the teachings of the cited references to create the invention of the instant claims with a reasonable expectation of success. It is noted that the recombinant bGM-CSF could be purified and used in the vaccine in its proteinaceous form, or the cDNA encoding bGM-CSF (taught by Baker) could be cloned into the bovine expression plasmid taught by Audonnet, which could then be with the vaccine complex to transfect and express bGM-CSF in bovine cells with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to add to a bovine vaccine composition bGM-CSF or a plasmid which encodes and expresses bGM-CSF in bovine cells because 1) GM-CSF was known to act as an adjuvant in vaccine compositions and 2) the prior art indicates that bGM-CSF could be used to augment immune responsiveness to infectious pathogens (i.e. could be an adjuvant).

Claims 84, 92, 94, 95, 100 and 108 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 5-8 of U.S. Patent No. 6,376,473 B1 (Audonnet) in view of U.S. Patent No. 6,586,409 B1 (Wheeler) and further in view of Li (WO 96/40945).

It is noted that the instant claims appear to be drawn to an improved vaccine for a bovine pathogen (BRSV) wherein the improvement comprises 1) the addition of a lipid complex (such as DMRIE/DOPE) to the vaccine (as mentioned above); 2) wherein a transmembrane of one of

the pathogens has been deleted; and 3) wherein the plasmid vaccine further comprises the intron II of the rabbit beta-globin gene as a stabilizing intron. However, it was known in the prior art that deleting the transmembrane portion of the BRSV-F gene and including the intron II of the rabbit beta-globin gene could improve the vaccine. Therefore, for the reasons set forth below, the instant claims are obvious in view of the prior art.

Claim 84 is obvious in view of the teachings of Audonnet and Wheeler as mentioned above.

As mentioned above, Audonnet teaches a BRSV plasmid vaccine and Wheeler teaches lipid complexes which can be used to increase plasmid uptake and also as an adjuvant in a vaccine composition.

Neither Audonnet nor Wheeler teaches that the vaccine composition comprises a BRSV pathogen wherein the pathogen has a transmembrane domain deleted.

Li teaches a nucleic acid RSV vaccine comprising a plasmid containing a nucleotide sequence which encodes an RSV F protein from which the transmembrane region is absent (see p. 5, lines 25-35). Li teaches that the deletion of the trans membrane region results in a secreted form of the RSV F protein (see p. 5, line 35 through p. 6, line 1). Li teaches deletion of the transmembrane domain increases the efficacy of the vaccine (see p. 27, lines 2-21). In fact, only the vaccine comprising the deletion of the transmembrane of the F protein result in complete protection (see p. 27, lines 14-21). Additionally the vaccine comprises the nucleotide sequence of the rabbit beta-globin intron II, to prevent aberrant mRNA splicing (see p. 6, lines 2-9). The rabbit beta-globin intron II sequence prevents aberrant mRNA splicing, thus stabilizing the mRNA and enhancing the immunoprotective ability of the vaccine (see p. 6, lines 26-32).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to combine the teachings of the cited references to create the invention of the instant claims with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to delete the transmembrane region of the BRSV-F gene and to include intron II or the rabbit beta-globin gene in the plasmid in order to enhance the immunoprotective ability of the vaccine, as taught by Li.

Claims 84, 93, 97, 98 and 104 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 5-8 of U.S. Patent No. 6,376,473 B1 (Audonnet) in view of U.S. Patent No. 6,586,409 B1 (Wheeler) and further in view of Choi et al. (Virology 1998, 250:230-240).

It is noted that the instant claims appear to be drawn to an improved vaccine for a bovine pathogen (BRSV) wherein the improvement comprises 1) the addition of a lipid complex (such as DMRIE/DOPE) to the vaccine (as mentioned above); 2) a substitution of the signal sequence with a heterologous tPA signal sequence. However, it was known in the prior art that the human tPA signal sequence could improve a vaccine. Therefore, for the reasons set forth below, the instant claims are obvious in view of the prior art.

Claim 84 is obvious in view of the teachings of Audonnet and Wheeler as mentioned above.

As mentioned above, Audonnet teaches a BRSV plasmid vaccine and Wheeler teaches lipid complexes which can be used to increase plasmid uptake and also as an adjuvant in a

vaccine composition. Audonnet specifically teaches that the vaccine can comprise plasmid(s) which encode and express BRSV-F and/or BRSV-G.

Neither Audonnet nor Wheeler teach that the plasmid vaccine comprises and expresses a heterologous tPA signal sequence in place of the normal signal sequence of BRSV-F or BRSV-G.

Choi teaches the human tPA signal sequence can enhance the expression of an immunogen and enhance the host's immune response to the immunogen when the immunogen is expressed as a tPA/immunogen fusion protein (see p. 233, Table 2 wherein the tPA/immunogen fusion (WRG/4) results in increased IgG response compared the wild-type immunogen (pcDNA/4)).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to combine the teachings of the cited references to create the invention of the instant claims with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to include a heterologous tPA signal sequence as a fusion with the pathogenic gene (substituting the normal BRSV-F or NRSV-G signal sequence with the human tPA signal sequence) in the plasmid in order to enhance the expression of the immunogen and enhance the host's immune response to the immunogen.

Claims 84-118 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 5-8 of U.S. Patent No. 6,376,473 B1 (Audonnet) in view of U.S. Patent No. 6,586,409 B1 (Wheeler) and further in view of Xiang et

al. (Immunity 1995, 2:129-135), Baker et al. (US Patent 5,106,733; 1992), Li (WO 96/40945), and Choi et al. (Virology 1998, 250:230-240).

It is noted that the invention appears to be an improved vaccine for a bovine pathogen (BRSV) wherein the improvement comprises: the addition of a lipid complex (such as DMRIE/DOPE) to the vaccine; the a gene encoding the BRSV-F gene with a substitution of a human tPA signal sequence in place of the normal signal sequence; a second plasmid encoding the BRSV-G gene with a substitution of a human tPA signal sequence in place of the normal signal sequence; bovine GM-CSF or a plasmid which expresses bGM-CSF in bovine cells; wherein the transmembrane signal sequence of the pathogenic gene is deleted; and a stabilizing intron, such as intron II of the rabbit beta-globin gene. As mentioned and summarized below, all of the modifications were known in the prior art. Therefore, for the reasons set forth below, the instant claims are obvious in view of the prior art.

Audonnet teaches a vaccine for BRSV comprising at least one plasmid that contains and expresses in vivo (in a bovine host cell) a nucleic acid molecule having sequences encoding BRSV-F, or BRSV-G or BRSV-F and –G proteins (e.g., see abstract and claims 5-8).

Audonnet does not teach that the BRSV vaccine comprises a cationic lipid, or a cationic lipid complex.

Wheeler teaches an adjuvant composition comprising a lipid or lipid complex (specifically DMRIE and DMRIE/DOPE, as well as GAP-DMRIE and DOPE) that can be used in combination with a DNA vaccine such as a plasmid vaccine wherein the lipid complex enhances the delivery and immune response to the polynucleotide-based vaccine. Specifically Wheeler teaches, "The adjuvant composition of the instant invention enhances the immune

response of the vertebrate to the immunogen." (See col. 2, lines 55-61); and , "The present invention, in contrast to the prior art, is useful for enhancing the humoral response of a vertebrate to a polynucleotide-based vaccine..." (See col. 3, lines 27-30). With respect to the term "vertebrate", Wheeler specifically indicates, "The term 'vertebrate' is intended to encompass a singular 'vertebrate' as well as plural 'vertebrates', and comprises mammalian and avian species as well as fish." (See col. 12, lines 35-40). Thus specifically indicating that the composition works in all mammals as well as fish and birds.

Neither Audonnet nor Wheeler teaches that the vaccine composition can comprise bovine GM-CSF or a plasmid encoding bovine GM-CSF.

Xiang teaches a method for enhancing the immune response to a DNA vaccine by co-administering a plasmid vaccine (here, a plasmid expressing the glycoprotein of rabies virus in vivo) and a plasmid expressing GM-CSF (here, mouse GM-CSF) (see p. 129, abstract; p. 130, Table 1; and p.132, under "A plasmid vector expressing mouse GM-CSF enhances the efficacy of the DNA vaccine to Rabies Virus). Xiang teaches that the mouse GM-CSF enhances the efficacy of the vaccine (see p. 132).

Xiang does not teach that the GM-GMCSF is bovine GM-CSF.

Baker teaches the cDNA sequence of bovine GM-CSF and methods of expressing bovine GM-CSF in a cell using an expression vector as well as methods for purifying the recombinant bovine GM-CSF (see Figure 1; column 1, lines 55-68; and column 6, line 13 through column 8, line 70). Baker teaches that bovine GM-CSF can be useful as "a therapeutic agent treating various cytopenias, and its apparent effect upon mature granulocytes and macrophages... [and] therapeutic compositions comprising recombinant bGM-CSF or active homologues could be

employed to augment immune responsiveness to infectious pathogens or to assist in reconstituting normal blood cell populations following viral infection or other conditions resulting in hematopoietic cell suppression." (See column 1, lines 41-53).

Audonnet, Wheeler, Xiang and Baker do not teach that the vaccine composition comprises a BRSV pathogen wherein the pathogen has a transmembrane domain deleted or that the plasmid contains a stabilizing intron such as intron II of the rabbit beta-globin gene.

Li teaches a nucleic acid RSV vaccine comprising a plasmid containing a nucleotide sequence which encodes an RSV F protein from which the transmembrane region is absent (see p. 5, lines 25-35). Li teaches that the deletion of the trans membrane region results in a secreted form of the RSV F protein (see p. 5, line 35 through p. 6, line 1). Li teaches deletion of the transmembrane domain increases the efficacy of the vaccine (see p. 27, lines 2-21). In fact, only the vaccine comprising the deletion of the transmembrane of the F protein result in complete protection (see p. 27, lines 14-21). Additionally the vaccine comprises the nucleotide sequence of the rabbit beta-globin intron II, to prevent aberrant mRNA splicing (see p. 6, lines 2-9). The rabbit beta-globin intron II sequence prevents aberrant mRNA splicing, thus stabilizing the mRNA and enhancing the immunoprotective ability of the vaccine (see p. 6, lines 26-32).

Audonnet, Wheeler, Xiang, Baker and Li do not teach that the vaccine composition comprises that the plasmid vaccine comprises and expresses a heterologous tPA signal sequence in place of the normal signal sequence of BRSV-F or BRSV-G.

Choi teaches Choi teaches the human tPA signal sequence can enhance the expression of an immunogen and enhance the host's immune response to the immunogen when the immunogen is expressed as a tPA/immunogen fusion protein (see p. 233, Table 2 wherein the

tPA/immunogen fusion (WRG/4) results in increased IgG response compared the wild-type immunogen (pcDNA/4)).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to combine the teachings of the cited references to create the invention of the instant claims with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to make the modifications in order to create a better vaccine which confers a greater immune response to pathogen(s) (here, BRSV-F and/or BRSV-G) resulting in a greater degree of protective immunity to the pathogen.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 84, 85, 96 and 116-118 are rejected under 35 U.S.C. 103(a) as being obvious over claims 5-8 of U.S. Patent No. 6,376,473 B1 (Audonnet) in view of in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).

It is noted that the invention appears to be an improved vaccine for a bovine pathogen (BRSV) wherein the improvement is the addition of a lipid complex (such as DMRIE/DOPE) to the vaccine. As mentioned below, a DNA plasmid vaccine for BRSV was known in the prior art (Audonnet) and the lipid complex DMRIE/DOPE was known to act as an

adjuvant as well as a facilitator of DNA delivery into cells (Klavinskis). Therefore, for the reasons set forth below, the instant claims are obvious in view of the prior art.

The claims are drawn to a DNA vaccine against BRSV comprising at least one plasmid that contains and expresses in a bovine host cell a nucleotide sequence encoding a BRSV immunogen and a cationic lipid (see claims 84, 85, 112, 118); wherein the vaccine further comprises DOPE (claims 85, 112); wherein the bovine pathogen is BRSV (see claim 96); wherein the immunogen is BRSV-F (claim 116) or BRSV-G (claim 118).

Audonnet teaches a vaccine for BRSV comprising at least one plasmid that contains and expresses in vivo (in a bovine host cell) a nucleic acid molecule having sequences encoding BRSV-F, or BRSV-G or BRSV-F and –G proteins (e.g., see abstract and claims 5-8).

Audonnet does not teach that the BRSV vaccine comprises the cationic lipid DMRIE or DOPE, or the cationic lipid complex DMRIE/DOPE.

Klavinskis teaches a plasmid DNA vaccine complexed with the lipid complex DMRIE/DOPE which results in the enhanced expression of the encoded protein when administered to the respiratory tract of an animal, and which results in the increased circulating levels of specific IgA and IgG (e.g., see abstract). Klavinskis specifically teaches, "Cytofectins [the DMRIE/DOPE complex] may also provide a secondary role as an adjuvant, facilitating uptake of plasmid DNA by APCs or creating inflammation." (See p. 259, second column). Therefore, Klavinskis teaches that the DMRIE/DOPE lipid complex can be useful for 1) increasing the uptake of plasmids—resulting in an increased expression of the encoded protein; and 2) as an adjuvant for increasing the immune response to pathogens.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to combine the teachings of Audonnet and Klavinskis to create the invention of the instant claims with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to combine the references in order to increase the uptake of the plasmid vaccine into the target cells—resulting in the increased expression of the encoded pathogens (here, BRSV-F and/or BRSV-G) and to stimulate the host's immune system in order to get an increased immune response against the pathogens.

Claims 84-91 rejected under 35 U.S.C. 103(a) as being obvious over claims 5-8 of U.S. Patent No. 6,376,473 B1 (Audonnet) in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Xiang et al. (Immunity 1995, 2:129-135), and Baker et al. (US Patent 5,106,733; 1992).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in

accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).

It is noted that the instant claims appear to be drawn to an improved vaccine for a bovine pathogen (BRSV) wherein the improvement is the addition of a lipid complex (such as DMRIE/DOPE) to the vaccine (as mentioned above) with the addition of bovine GM-CSF or a plasmid encoding bovine GM-CSF to the vaccine. However, GM-CSF was known to act as an adjuvant for vaccine compositions. Therefore, for the reasons set forth below, the instant claims are obvious in view of the prior art.

Claims 84 and 85 are obvious in view of the teachings of Audonnet and Klavinskis as mentioned above.

As mentioned above, Audonnet teaches a BRSV plasmid vaccine and Klavinskis teaches that DMRIE/DOPE lipid complexes which can be used to increase plasmid uptake and also as an adjuvant in a vaccine composition.

Neither Audonnet nor Klavinskis teach that the vaccine composition can comprise bovine GM-CSF or a plasmid encoding bovine GM-CSF.

Xiang teaches a method for enhancing the immune response to a DNA vaccine by co-administering a plasmid vaccine (here, a plasmid expressing the glycoprotein of rabies virus in vivo) and a plasmid expressing GM-CSF (here, mouse GM-CSF) (see p. 129, abstract; p. 130, Table 1; and p.132, under "A plasmid vector expressing mouse GM-CSF enhances the efficacy

of the DNA vaccine to Rabies Virus). Xiang teaches that the mouse GM-CSF enhances the efficacy of the vaccine (see p. 132).

Xiang does not teach that the GM-GMCSF is bovine GM-CSF.

Baker teaches the cDNA sequence of bovine GM-CSF and methods of expressing bovine GM-CSF in a cell using an expression vector as well as methods for purifying the recombinant bovine GM-CSF (see Figure 1; column 1, lines 55-68; and column 6, line 13 through column 8, line 70). Baker teaches that bovine GM-CSF can be useful as "a therapeutic agent treating various cytopenias, and its apparent effect upon mature granulocytes and macrophages... [and] therapeutic compositions comprising recombinant bGM-CSF or active homologues could be employed to augment immune responsiveness to infectious pathogens or to assist in reconstituting normal blood cell populations following viral infection or other conditions resulting in hematopoietic cell suppression." (See column 1, lines 41-53).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to combine the teachings of the cited references to create the invention of the instant claims with a reasonable expectation of success. It is noted that the recombinant bGM-CSF could be purified and used in the vaccine in its proteinaceous form, or the cDNA encoding bGM-CSF (taught by Baker) could be cloned into the bovine expression plasmid taught by Audonnet, which could then be with the vaccine complex to transfect and express bGM-CSF in bovine cells with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to add to a bovine vaccine composition bGM-CSF or a plasmid which encodes and expresses bGM-CSF in bovine cells because 1) GM-CSF was known to act as an adjuvant in vaccine compositions and 2) the prior

art indicates that bGM-CSF could be used to augment immune responsiveness to infectious pathogens (i.e. could be an adjuvant).

Claims 84, 92, 94, 95, 100 and 108 rejected under 35 U.S.C. 103(a) as being obvious over claims 5-8 of U.S. Patent No. 6,376,473 B1 (Audonnet) in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Li (WO 96/40945).

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It is noted that the instant claims appear to be drawn to an improved vaccine for a bovine pathogen (BRSV) wherein the improvement comprises 1) the addition of a lipid complex (such as DMRIE/DOPE) to the vaccine (as mentioned above); 2) wherein a transmembrane of one of the pathogens has been deleted; and 3) wherein the plasmid vaccine further comprises the intron II of the rabbit beta-globin gene as a stabilizing intron. However, it was known in the prior art that deleting the transmembrane portion of the BRSV-F gene and including the intron II of the rabbit beta-globin gene could improve the vaccine. Therefore, for the reasons set forth below, the instant claims are obvious in view of the prior art.

Claim 84 is obvious in view of the teachings of Audonnet and Klavinskis as mentioned above.

As mentioned above, Audonnet teaches a BRSV plasmid vaccine and Klavinskis teaches that DMRIE/DOPE lipid complexes which can be used to increase plasmid uptake and also as an adjuvant in a vaccine composition.

Neither Audonnet nor Klavinskis teach that the vaccine composition comprises a BRSV pathogen wherein the pathogen has a transmembrane domain deleted.

Li teaches a nucleic acid RSV vaccine comprising a plasmid containing a nucleotide sequence which encodes an RSV F protein from which the transmembrane region is absent (see p. 5, lines 25-35). Li teaches that the deletion of the trans membrane region results in a secreted form of the RSV F protein (see p. 5, line 35 through p. 6, line 1). Li teaches deletion of the transmembrane domain increases the efficacy of the vaccine (see p. 27, lines 2-21). In fact, only the vaccine comprising the deletion of the transmembrane of the F protein result in complete protection (see p. 27, lines 14-21). Additionally the vaccine comprises the nucleotide sequence

of the rabbit beta-globin intron II, to prevent aberrant mRNA splicing (see p. 6, lines 2-9). The rabbit beta-globin intron II sequence prevents aberrant mRNA splicing, thus stabilizing the mRNA and enhancing the immunoprotective ability of the vaccine (see p. 6, lines 26-32).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to combine the teachings of the cited references to create the invention of the instant claims with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to delete the transmembrane region of the BRSV-F gene and to include intron II or the rabbit beta-globin gene in the plasmid in order to enhance the immunoprotective ability of the vaccine, as taught by Li.

Claims 84, 93, 97, 98 and 104 are rejected under 35 U.S.C. 103(a) as being obvious over claims 5-8 of U.S. Patent No. 6,376,473 B1 (Audonnet) in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Choi et al. (Virology 1998, 250:230-240).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the

application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).

It is noted that the instant claims appear to be drawn to an improved vaccine for a bovine pathogen (BRSV) wherein the improvement comprises 1) the addition of a lipid complex (such as DMRIE/DOPE) to the vaccine (as mentioned above); 2) a substitution of the signal sequence with a heterologous tPA signal sequence. However, it was known in the prior art that the human tPA signal sequence could improve a vaccine. Therefore, for the reasons set forth below, the instant claims are obvious in view of the prior art.

Claim 84 is obvious in view of the teachings of Audonnet and Klavinskis as mentioned above.

As mentioned above, Audonnet teaches a BRSV plasmid vaccine and Klavinskis teaches that DMRIE/DOPE lipid complexes which can be used to increase plasmid uptake and also as an adjuvant in a vaccine composition. Audonnet specifically teaches that the vaccine can comprise plasmid(s) which encode and express BRSV-F and/or BRSV-G.

Neither Audonnet nor Klavinskis teach that the plasmid vaccine comprises and expresses a heterologous tPA signal sequence in place of the normal signal sequence of BRSV-F or BRSV-G.

Choi teaches the human tPA signal sequence can enhance the expression of an immunogen and enhance the host's immune response to the immunogen when the immunogen is expressed as a tPA/immunogen fusion protein (see p. 233, Table 2 wherein the tPA/immunogen fusion (WRG/4) results in increased IgG response compared the wild-type immunogen (pcDNA/4)).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to combine the teachings of the cited references to create the invention of the instant claims with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to include a heterologous tPA signal sequence as a fusion with the pathogenic gene (substituting the normal BRSV-F or NRSV-G signal sequence with the human tPA signal sequence) in the plasmid in order to enhance the expression of the immunogen and enhance the host's immune response to the immunogen.

Claims 84-118 are rejected under 35 U.S.C. 103(a) as being obvious over claims 5-8 of U.S. Patent No. 6,376,473 B1 (Audonnet) in view of Klavinskis et al. (J. Immunol. Vol. 162, No. 1, pages 254-262; January 1, 1999) and further in view of Xiang et al. (Immunity 1995, 2:129-135), Baker et al. (US Patent 5,106,733; 1992), Li (WO 96/40945), and Choi et al. (Virology 1998, 250:230-240).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the

inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).

It is noted that the invention appears to be an improved vaccine for a bovine pathogen (BRSV) wherein the improvement comprises: the addition of a lipid complex (such as DMRIE/DOPE) to the vaccine; the a gene encoding the BRSV-F gene with a substitution of a human tPA signal sequence in place of the normal signal sequence; a second plasmid encoding the BRSV-G gene with a substitution of a human tPA signal sequence in place of the normal signal sequence; bovine GM-CSF or a plasmid which expresses bGM-CSF in bovine cells; wherein the transmembrane signal sequence of the pathogenic gene is deleted; and a stabilizing intron, such as intron II of the rabbit beta-globin gene. As mentioned and summarized below, all of the modifications were known in the prior art. Therefore, for the reasons set forth below, the instant claims are obvious in view of the prior art.

Audonnet teaches a vaccine for BRSV comprising at least one plasmid that contains and expresses in vivo (in a bovine host cell) a nucleic acid molecule having sequences encoding BRSV-F, or BRSV-G or BRSV-F and –G proteins (e.g., see abstract and claims 5-8).

Audonnet does not teach that the BRSV vaccine comprises a cationic lipid, or a cationic lipid complex.

Klavinskis teaches a plasmid DNA vaccine complexed with the lipid DMRIE/DOPE which results in the enhanced expression of the encoded protein when administered to the respiratory tract of an animal, and which results in the increased circulating levels of specific IgA and IgG (e.g., see abstract). Klavinskis specifically teaches, "Cytofectins [the DMRIE/DOPE complex] may also provide a secondary role as an adjuvant, facilitating uptake of plasmid DNA by APCs or creating inflammation." (See p. 259, second column). Therefore, Klavinskis teaches that the DMRIE/DOPE lipid complex can be useful for 1) increasing the uptake of plasmids—resulting in an increased expression of the encoded protein; and 2) as an adjuvant for increasing the immune response to pathogens.

Neither Audonnet nor Klavinskis teaches that the vaccine composition can comprise bovine GM-CSF or a plasmid encoding bovine GM-CSF.

Xiang teaches a method for enhancing the immune response to a DNA vaccine by co-administering a plasmid vaccine (here, a plasmid expressing the glycoprotein of rabies virus in vivo) and a plasmid expressing GM-CSF (here, mouse GM-CSF) (see p. 129, abstract; p. 130, Table 1; and p.132, under "A plasmid vector expressing mouse GM-CSF enhances the efficacy of the DNA vaccine to Rabies Virus). Xiang teaches that the mouse GM-CSF enhances the efficacy of the vaccine (see p. 132).

Xiang does not teach that the GM-GMCSF is bovine GM-CSF.

Baker teaches the cDNA sequence of bovine GM-CSF and methods of expressing bovine GM-CSF in a cell using an expression vector as well as methods for purifying the recombinant bovine GM-CSF (see Figure 1; column 1, lines 55-68; and column 6, line 13 through column 8, line 70). Baker teaches that bovine GM-CSF can be useful as "a therapeutic agent treating various cytopenias, and its apparent effect upon mature granulocytes and macrophages... [and] therapeutic compositions comprising recombinant bGM-CSF or active homologues could be employed to augment immune responsiveness to infectious pathogens or to assist in reconstituting normal blood cell populations following viral infection or other conditions resulting in hematopoietic cell suppression." (See column 1, lines 41-53).

Audonnet, Klavinskis, Xiang and Baker do not teach that the vaccine composition comprises a BRSV pathogen wherein the pathogen has a transmembrane domain deleted or that the plasmid contains a stabilizing intron such as intron II of the rabbit beta-globin gene.

Li teaches a nucleic acid RSV vaccine comprising a plasmid containing a nucleotide sequence which encodes an RSV F protein from which the transmembrane region is absent (see p. 5, lines 25-35). Li teaches that the deletion of the trans membrane region results in a secreted form of the RSV F protein (see p. 5, line 35 through p. 6, line 1). Li teaches deletion of the transmembrane domain increases the efficacy of the vaccine (see p. 27, lines 2-21). In fact, only the vaccine comprising the deletion of the transmembrane of the F protein result in complete protection (see p. 27, lines 14-21). Additionally the vaccine comprises the nucleotide sequence of the rabbit beta-globin intron II, to prevent aberrant mRNA splicing (see p. 6, lines 2-9). The

rabbit beta-globin intron II sequence prevents aberrant mRNA splicing, thus stabilizing the mRNA and enhancing the immunoprotective ability of the vaccine (see p. 6, lines 26-32).

Audonnet, Klavinskis, Xiang, Baker and Li do not teach that the vaccine composition comprises that the plasmid vaccine comprises and expresses a heterologous tPA signal sequence in place of the normal signal sequence of BRSV-F or BRSV-G.

Choi teaches Choi teaches the human tPA signal sequence can enhance the expression of an immunogen and enhance the host's immune response to the immunogen when the immunogen is expressed as a tPA/immunogen fusion protein (see p. 233, Table 2 wherein the tPA/immunogen fusion (WRG/4) results in increased IgG response compared the wild-type immunogen (pcDNA/4)).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to combine the teachings of the cited references to create the invention of the instant claims with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to make the modifications in order to create a better vaccine which confers a greater immune response to pathogen(s) (here, BRSV-F and/or BRSV-G) resulting in a greater degree of protective immunity to the pathogen.

Claims 84, 85, 96 and 116-118 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 5-8 of U.S. Patent No. 6,376,473 B1 (Audonnet) in view of U.S. Patent No. 6,586,409 B1 (Wheeler).

It is noted that the invention appears to be an improved vaccine for a bovine pathogen (BRSV) wherein the improvement is the addition of a lipid complex (such as DMRIE/DOPE) to

the vaccine. As mentioned below, a DNA plasmid vaccine for BRSV was known in the prior art (Audonnet) and the lipid complex DMRIE/DOPE was known to act as an adjuvant as well as a facilitator of DNA delivery into cells (Klavinskis). Therefore, for the reasons set forth below, the instant claims are obvious in view of the prior art.

The claims are drawn to a DNA vaccine against BRSV comprising at least one plasmid that contains and expresses in a bovine host cell a nucleotide sequence encoding a BRSV immunogen and a cationic lipid (see claims 84, 85, 112, 118); wherein the vaccine further comprises DOPE (claims 85, 112); wherein the bovine pathogen is BRSV (see claim 96); wherein the immunogen is BRSV-F (claim 116) or BRSV-G (claim 118).

Audonnet teaches a vaccine for BRSV comprising at least one plasmid that contains and expresses in vivo (in a bovine host cell) a nucleic acid molecule having sequences encoding BRSV-F, or BRSV-G or BRSV-F and –G proteins (e.g., see abstract and claims 5-8).

Audonnet does not teach that the BRSV vaccine comprises the cationic lipid DMRIE or DOPE, or the cationic lipid complex DMRIE/DOPE.

Wheeler teaches an adjuvant composition comprising a lipid or lipid complex (specifically DMRIE and DMRIE/DOPE, as well as GAP-DMRIE and DOPE) that can be used in combination with a DNA vaccine such as a plasmid vaccine wherein the lipid complex enhances the delivery and immune response to the polynucleotide-based vaccine. Specifically Wheeler teaches, "The adjuvant composition of the instant invention enhances the immune response of the vertebrate to the immunogen." (See col. 2, lines 55-61); and , "The present invention, in contrast to the prior art, is useful for enhancing the humoral response of a vertebrate to a polynucleotide-based vaccine..." (See col. 3, lines 27-30). With respect to the term

"vertebrate", Wheeler specifically indicates, "The term 'vertebrate' is intended to encompass a singular 'vertebrate' as well as plural 'vertebrates', and comprises mammalian and avian species as well as fish." (See col. 12, lines 35-40). Thus specifically indicating that the composition works in all mammals as well as fish and birds.

Therefore, it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to combine the teachings of Audonnet and Wheeler to create the invention of the instant claims with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to combine the references in order to increase the uptake of the plasmid vaccine into the target cells—resulting in the increased expression of the encoded pathogens (here, BRSV-F and/or BRSV-G) and to stimulate the host's immune system in order to get an increased immune response against the pathogens.

Claims 84-91 remain rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 5-8 of U.S. Patent No. 6,376,473 B1 (Audonnet) in view of U.S. Patent No. 6,586,409 B1 (Wheeler) and further in view of Xiang et al. (Immunity 1995, 2:129-135), and Baker et al. (US Patent 5,106,733; 1992) for the reasons of record.

It is noted that the instant claims appear to be drawn to an improved vaccine for a bovine pathogen (BRSV) wherein the improvement is the addition of a lipid complex (such as DMRIE/DOPE) to the vaccine (as mentioned above) with the addition of bovine GM-CSF or a plasmid encoding bovine GM-CSF to the vaccine. However, GM-CSF was known to act as an

adjuvant for vaccine compositions. Therefore, for the reasons set forth below, the instant claims are obvious in view of the prior art.

Claims 84 and 85 are obvious in view of the teachings of Audonnet and Wheeler as mentioned above.

As mentioned above, Audonnet teaches a BRSV plasmid vaccine and Wheeler teaches lipid complexes which can be used to increase plasmid uptake and also as an adjuvant in a vaccine composition.

Neither Audonnet nor Wheeler teaches that the vaccine composition can comprise bovine GM-CSF or a plasmid encoding bovine GM-CSF.

Xiang teaches a method for enhancing the immune response to a DNA vaccine by co-administering a plasmid vaccine (here, a plasmid expressing the glycoprotein of rabies virus in vivo) and a plasmid expressing GM-CSF (here, mouse GM-CSF) (see p. 129, abstract; p. 130, Table 1; and p.132, under "A plasmid vector expressing mouse GM-CSF enhances the efficacy of the DNA vaccine to Rabies Virus). Xiang teaches that the mouse GM-CSF enhances the efficacy of the vaccine (see p. 132).

Xiang does not teach that the GM-GMCSF is bovine GM-CSF.

Baker teaches the cDNA sequence of bovine GM-CSF and methods of expressing bovine GM-CSF in a cell using an expression vector as well as methods for purifying the recombinant bovine GM-CSF (see Figure 1; column 1, lines 55-68; and column 6, line 13 through column 8, line 70). Baker teaches that bovine GM-CSF can be useful as "a therapeutic agent treating various cytopenias, and its apparent effect upon mature granulocytes and macrophages... [and] therapeutic compositions comprising recombinant bGM-CSF or active homologues could be

employed to augment immune responsiveness to infectious pathogens or to assist in reconstituting normal blood cell populations following viral infection or other conditions resulting in hematopoietic cell suppression." (See column 1, lines 41-53).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to combine the teachings of the cited references to create the invention of the instant claims with a reasonable expectation of success. It is noted that the recombinant bGM-CSF could be purified and used in the vaccine in its proteinaceous form, or the cDNA encoding bGM-CSF (taught by Baker) could be cloned into the bovine expression plasmid taught by Audonnet, which could then be with the vaccine complex to transfect and express bGM-CSF in bovine cells with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to add to a bovine vaccine composition bGM-CSF or a plasmid which encodes and expresses bGM-CSF in bovine cells because 1) GM-CSF was known to act as an adjuvant in vaccine compositions and 2) the prior art indicates that bGM-CSF could be used to augment immune responsiveness to infectious pathogens (i.e. could be an adjuvant).

Claims 84, 92, 94, 95, 100 and 108 are rejected under 35 U.S.C. 103(a) as being obvious over claims 5-8 of U.S. Patent No. 6,376,473 B1 (Audonnet) in view of U.S. Patent No. 6,586,409 B1 (Wheeler) and further in view of Li (WO 96/40945).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37

CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).

It is noted that the instant claims appear to be drawn to an improved vaccine for a bovine pathogen (BRSV) wherein the improvement comprises 1) the addition of a lipid complex (such as DMRIE/DOPE) to the vaccine (as mentioned above); 2) wherein a transmembrane of one of the pathogens has been deleted; and 3) wherein the plasmid vaccine further comprises the intron II of the rabbit beta-globin gene as a stabilizing intron. However, it was known in the prior art that deleting the transmembrane portion of the BRSV-F gene and including the intron II of the rabbit beta-globin gene could improve the vaccine. Therefore, for the reasons set forth below, the instant claims are obvious in view of the prior art.

Claim 84 is obvious in view of the teachings of Audonnet and Wheeler as mentioned above.

As mentioned above, Audonnet teaches a BRSV plasmid vaccine and Wheeler teaches lipid complexes which can be used to increase plasmid uptake and also as an adjuvant in a vaccine composition.

Neither Audonnet nor Wheeler teaches that the vaccine composition comprises a BRSV pathogen wherein the pathogen has a transmembrane domain deleted.

Li teaches a nucleic acid RSV vaccine comprising a plasmid containing a nucleotide sequence which encodes an RSV F protein from which the transmembrane region is absent (see p. 5, lines 25-35). Li teaches that the deletion of the trans membrane region results in a secreted form of the RSV F protein (see p. 5, line 35 through p. 6, line 1). Li teaches deletion of the transmembrane domain increases the efficacy of the vaccine (see p. 27, lines 2-21). In fact, only the vaccine comprising the deletion of the transmembrane of the F protein result in complete protection (see p. 27, lines 14-21). Additionally the vaccine comprises the nucleotide sequence of the rabbit beta-globin intron II, to prevent aberrant mRNA splicing (see p. 6, lines 2-9). The rabbit beta-globin intron II sequence prevents aberrant mRNA splicing, thus stabilizing the mRNA and enhancing the immunoprotective ability of the vaccine (see p. 6, lines 26-32).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to combine the teachings of the cited references to create the invention of the instant claims with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to delete the transmembrane region of the BRSV-F gene and to include intron II or the rabbit beta-globin gene in the plasmid in order to enhance the immunoprotective ability of the vaccine, as taught by Li.

Claims 84, 93, 97, 98 and 104 are rejected under 35 U.S.C. 103(a) as being obvious over claims 5-8 of U.S. Patent No. 6,376,473 B1 (Audonnet) in view of U.S. Patent No. 6,586,409 B1 (Wheeler) and further in view of Choi et al. (Virology 1998, 250:230-240).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).

It is noted that the instant claims appear to be drawn to an improved vaccine for a bovine pathogen (BRSV) wherein the improvement comprises 1) the addition of a lipid complex (such as DMRIE/DOPE) to the vaccine (as mentioned above); 2) a substitution of the signal sequence

with a heterologous tPA signal sequence. However, it was known in the prior art that the human tPA signal sequence could improve a vaccine. Therefore, for the reasons set forth below, the instant claims are obvious in view of the prior art.

Claim 84 is obvious in view of the teachings of Audonnet and Wheeler as mentioned above.

As mentioned above, Audonnet teaches a BRSV plasmid vaccine and Wheeler teaches lipid complexes which can be used to increase plasmid uptake and also as an adjuvant in a vaccine composition. Audonnet specifically teaches that the vaccine can comprise plasmid(s) which encode and express BRSV-F and/or BRSV-G.

Neither Audonnet nor Wheeler teach that the plasmid vaccine comprises and expresses a heterologous tPA signal sequence in place of the normal signal sequence of BRSV-F or BRSV-G.

Choi teaches the human tPA signal sequence can enhance the expression of an immunogen and enhance the host's immune response to the immunogen when the immunogen is expressed as a tPA/immunogen fusion protein (see p. 233, Table 2 wherein the tPA/immunogen fusion (WRG/4) results in increased IgG response compared the wild-type immunogen (pcDNA/4)).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to combine the teachings of the cited references to create the invention of the instant claims with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to include a heterologous tPA signal sequence as a fusion with the pathogenic gene (substituting the normal BRSV-F or NRSV-

G signal sequence with the human tPA signal sequence) in the plasmid in order to enhance the expression of the immunogen and enhance the host's immune response to the immunogen.

Claims 84-118 are rejected under 35 U.S.C. 103(a) as being obvious over claims 5-8 of U.S. Patent No. 6,376,473 B1 (Audonnet) in view of U.S. Patent No. 6,586,409 B1 (Wheeler) and further in view of Xiang et al. (Immunity 1995, 2:129-135), Baker et al. (US Patent 5,106,733; 1992), Li (WO 96/40945), and Choi et al. (Virology 1998, 250:230-240).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or

subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).

It is noted that the invention appears to be an improved vaccine for a bovine pathogen (BRSV) wherein the improvement comprises: the addition of a lipid complex (such as DMRIE/DOPE) to the vaccine; the a gene encoding the BRSV-F gene with a substitution of a human tPA signal sequence in place of the normal signal sequence; a second plasmid encoding the BRSV-G gene with a substitution of a human tPA signal sequence in place of the normal signal sequence; bovine GM-CSF or a plasmid which expresses bGM-CSF in bovine cells; wherein the transmembrane signal sequence of the pathogenic gene is deleted; and a stabilizing intron, such as intron II of the rabbit beta-globin gene. As mentioned and summarized below, all of the modifications were known in the prior art. Therefore, for the reasons set forth below, the instant claims are obvious in view of the prior art.

Audonnet teaches a vaccine for BRSV comprising at least one plasmid that contains and expresses in vivo (in a bovine host cell) a nucleic acid molecule having sequences encoding BRSV-F, or BRSV-G or BRSV-F and –G proteins (e.g., see abstract and claims 5-8).

Audonnet does not teach that the BRSV vaccine comprises a cationic lipid, or a cationic lipid complex.

Wheeler teaches an adjuvant composition comprising a lipid or lipid complex (specifically DMRIE and DMRIE/DOPE, as well as GAP-DMRIE and DOPE) that can be used in combination with a DNA vaccine such as a plasmid vaccine wherein the lipid complex enhances the delivery and immune response to the polynucleotide-based vaccine. Specifically Wheeler teaches, "The adjuvant composition of the instant invention enhances the immune

response of the vertebrate to the immunogen." (See col. 2, lines 55-61); and , "The present invention, in contrast to the prior art, is useful for enhancing the humoral response of a vertebrate to a polynucleotide-based vaccine..." (See col. 3, lines 27-30). With respect to the term "vertebrate", Wheeler specifically indicates, "The term 'vertebrate' is intended to encompass a singular 'vertebrate' as well as plural 'vertebrates', and comprises mammalian and avian species as well as fish." (See col. 12, lines 35-40). Thus specifically indicating that the composition works in all mammals as well as fish and birds.

Neither Audonnet nor Wheeler teaches that the vaccine composition can comprise bovine GM-CSF or a plasmid encoding bovine GM-CSF.

Xiang teaches a method for enhancing the immune response to a DNA vaccine by co-administering a plasmid vaccine (here, a plasmid expressing the glycoprotein of rabies virus in vivo) and a plasmid expressing GM-CSF (here, mouse GM-CSF) (see p. 129, abstract; p. 130, Table 1; and p.132, under "A plasmid vector expressing mouse GM-CSF enhances the efficacy of the DNA vaccine to Rabies Virus). Xiang teaches that the mouse GM-CSF enhances the efficacy of the vaccine (see p. 132).

Xiang does not teach that the GM-GMCSF is bovine GM-CSF.

Baker teaches the cDNA sequence of bovine GM-CSF and methods of expressing bovine GM-CSF in a cell using an expression vector as well as methods for purifying the recombinant bovine GM-CSF (see Figure 1; column 1, lines 55-68; and column 6, line 13 through column 8, line 70). Baker teaches that bovine GM-CSF can be useful as "a therapeutic agent treating various cytopenias, and its apparent effect upon mature granulocytes and macrophages... [and] therapeutic compositions comprising recombinant bGM-CSF or active homologues could be

employed to augment immune responsiveness to infectious pathogens or to assist in reconstituting normal blood cell populations following viral infection or other conditions resulting in hematopoietic cell suppression." (See column 1, lines 41-53).

Audonnet, Wheeler, Xiang and Baker do not teach that the vaccine composition comprises a BRSV pathogen wherein the pathogen has a transmembrane domain deleted or that the plasmid contains a stabilizing intron such as intron II of the rabbit beta-globin gene.

Li teaches a nucleic acid RSV vaccine comprising a plasmid containing a nucleotide sequence which encodes an RSV F protein from which the transmembrane region is absent (see p. 5, lines 25-35). Li teaches that the deletion of the trans membrane region results in a secreted form of the RSV F protein (see p. 5, line 35 through p. 6, line 1). Li teaches deletion of the transmembrane domain increases the efficacy of the vaccine (see p. 27, lines 2-21). In fact, only the vaccine comprising the deletion of the transmembrane of the F protein result in complete protection (see p. 27, lines 14-21). Additionally the vaccine comprises the nucleotide sequence of the rabbit beta-globin intron II, to prevent aberrant mRNA splicing (see p. 6, lines 2-9). The rabbit beta-globin intron II sequence prevents aberrant mRNA splicing, thus stabilizing the mRNA and enhancing the immunoprotective ability of the vaccine (see p. 6, lines 26-32).

Audonnet, Wheeler, Xiang, Baker and Li do not teach that the vaccine composition comprises that the plasmid vaccine comprises and expresses a heterologous tPA signal sequence in place of the normal signal sequence of BRSV-F or BRSV-G.

Choi teaches Choi teaches the human tPA signal sequence can enhance the expression of an immunogen and enhance the host's immune response to the immunogen when the immunogen is expressed as a tPA/immunogen fusion protein (see p. 233, Table 2 wherein the

tPA/immunogen fusion (WRG/4) results in increased IgG response compared the wild-type immunogen (pcDNA/4)).

Therefore it would have been prima facie obvious to one of ordinary skill in the art at the time of filing to combine the teachings of the cited references to create the invention of the instant claims with a reasonable expectation of success.

One of ordinary skill in the art would have been motivated to make the modifications in order to create a better vaccine which confers a greater immune response to pathogen(s) (here, BRSV-F and/or BRSV-G) resulting in a greater degree of protective immunity to the pathogen.

Response to Arguments

Applicant's arguments filed 6/25/04 have been fully considered but they are not persuasive.

Applicants argue that the Examiner is using hindsight reasoning, and there would have been no reasonable expectation of success when all of the needed teachings are combined. Specifically, Applicants argue that the prior art indicates that there are a number of problems with respect to the use of adjuvants for increasing an immune response in a host. Applicants argue that the cited prior art indicates that the successful use of adjuvants depends on many factors such as the particular antigen it is used in combination with as well as the routes of administration, species of animal used, etc. (e.g., see applicants arguments filed 6/25/04).

However, Applicants' arguments are not persuasive because all of the references cited by the applicants are directed to the use of traditional adjuvants, which does not include lipid adjuvants, as is required by the claims and which is also taught in the prior art (e.g., Klavinskis

and Wheeler). Therefore, Applicants arguments do not overcome the rejections of record because the prior art cited (Klavinskis and Wheeler) teach the use of lipid adjuvants in combination with polynucleotide-based vaccines. Klavinskis and Wheeler indicate that the lipid adjuvant not only increases the delivery of the vaccine to the cells, but also increases the host's immune response to the antigen, thus providing two distinct advantages for using lipid adjuvants over traditional adjuvants. Furthermore, Wheeler also clearly indicates that the lipid complex adjuvant can be used in all mammalian species, as well as fish and bird species. Therefore, the prior art teaches that lipid complexes including DMRIE/DOPE can be used to increase the delivery of polynucleotide-based vaccines as well as increase the host's immune response to the antigen encoded by the polynucleotide vaccine in mammalian species (which includes bovines and porcines). The Applicants have not offered any evidence to indicate that lipid adjuvants taught by Klavinskis and Wheeler would not work in larger mammals such as bovines or porcines. Considering the prior art specifically teaches that the lipid adjuvants encompassed by the claims are improved adjuvants compared to traditional adjuvants and can be used as adjuvants in all mammals as well as non-mammal species (birds/fish), Applicants arguments are not found to be persuasive.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon Eric Angell whose telephone number is 571-272-0756. The examiner can normally be reached on Mon-Fri, with every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader can be reached on 571-272-0760. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Jon Eric Angell, Ph.D.
Art unit 1635

DAVE T. NGUYEN
PRIMARY EXAMINER